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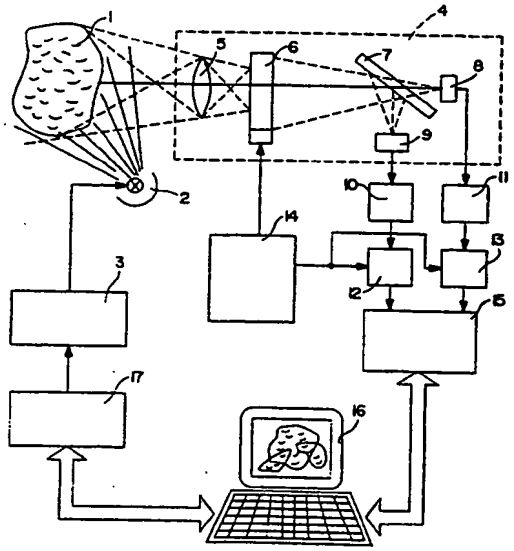
(57) Abstract

The invention relates to methods and apparatus for obtaining information on physiological processes taking place in living organisms. The method includes recording image sequences of living organism's skin area (1) in its own infrared radiation and using in visual light employing external illumination. At each point of the investigated skin area (1) the ratio between temporal changes in brightness for the image is determined. The apparatus includes a common optical system (4), photoelectric transformers coupled with a computer (16). An illuminator (2) with controlled spectral parameters is also connected with teh computer (16).



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APPARATUS FOR AND METHOD OF INVESTIGATING MICROCIRCULATION DYNAMICS

The technology field

The invention relates to the field of medicine, exactly, to methods and apparatus destined for obtaining information on physiological processes, taking place in living organism, it could be used as an up-to-day non- invasive method of diagnostics of early pathology precursors under population screening and for development of preventive medicine.

The preceding level of the technology

Functional dynamics of microcirculation of physiological liquids (blood, lymph, water etc.) in skin reflects the general functioning state of the main distributed physiological systems, such as cell metabolism, maintaining tissue energetic, and microcirculation, securing their metabolic resource. Functional status of these main life protecting tissue systems is determined by distributed regulation mechanisms: both the whole- organism - reflective and humoral - ones and local - metabolic one. Cell metabolism is connected with microcirculation via one else important distributed tissue system - that of perfusion. Functional dynamics of the latter interconnects two former systems.

The state of the whole-organism regulation systems is reflected not only the tissue functional dynamics at separate points of living organism, but mainly in the degree and the character of the spatial connectivity of this dynamics. To reveal the tissue physiological processes connectivity, investigation of continuous distribution of microcirculation functional dynamics and cell metabolism is necessary to perform. For instance, at the state of relaxation the spatial connectivity is minimal, while under stress conditions it is greatly increased. For malignant tissues an increased internal connectivity is peculiar as compared with the surrounding normal tissues. The state of all the whole- organism systems and organs is reflected in the spatial organization of the organism tissue functioning, since they appeared in course of evolution just to support the tissue functional status.

Up-to-day methods of living organism physical fields recording make it possible to follow the dynamics of these complicated physiological processes. These fields include first of all those characterizing the dynamic temperature "portrait" of the organism: radio-thermal, acousto-thermal and infrared radiation of the skin covers [1]. Each of the radiations brings information about processes, taking place inside the organism, from its own depth, determined by the tissue transparency for the concrete type of radiation. Thus, the skin covers shining brightly at the middle infrared (IR) range of 3 - 20 um, and this thermal radiation has maximal intensity at 8 - 14 um wavelength range. The characteristic probing depth in this case is about 100 um. The temperature of this layer is modulated by a network of capillary blood flow (microcirculation) in skin. Therefore brightness of the skin covers thermal radiation reflects a reach functional life of skin capillary blood flow - one of the main thermo-regulation mechanism of living organism.

However, the employment of the organism own IR-radiation is expedient only for those investigations when only relatively slow processes of the skin capillary blood functioning are recorded, since the characteristic thermo-projecting time from the depth of about 0.5 mm, where the nearest capillary layer is located, to the radiating surface layer (about 100 um) makes up to several seconds.

Larger probing depth, and consequently, higher time resolution, is characteristic of an active system of instigating of blood distribution at the near surface tissues, employing illumination by optical radiation [2], an optical picture at the near IR-red range is recorded in such a case. Temporally and spectrally dynamic picture of back scattered radiation, coming from the depths of up to 1 cm, appears in such a case which characterizes functional redistribution of physiological pigments, different haemoglobin forms, first of all. Thus, at 0.6 - 1.3 um (at longer wavelengths water-containing tissues are not transparent due to strong absorption of optical radiation by water) dynamic images in a real time reflect functional microcirculation and cell metabolism dynamics (via the corresponding optical absorption bands of haemoglobin and cytochrome aa3) and permit, thereby, revealing the earliest functional disturbances. Optical radiation used in such a case is quite near to the natural background illumination both by the intensity and spectral composition.

However, this method has a number of disadvantages. Back scattering measurements of optical radiation give information only on less dynamic physiological parameter - blood content (but not arterial blood flow, as in IR-thermovision), the method is also less sensitive to the inflammatory processes at the near surface tissues connected with extra thermo-production, all this limits the possibilities of revealing and identification of the functional disturbances at the capillary network of tissue blood supply.

The possibilities of a method for investigation of skin microcirculation functional dynamics can be expanded by recording of living organism area images at several spectral regions, or exactly, at 10-12 um range of the own IR-radiation and at visible spectral range, which permits to superimpose the images at monitor display and to add the details of one image with those of the other one [3]. Under these conditions, the image, obtained at the optical spectral range, is represented at the display as a monochrome one, and the superimposed IR-thermal image, is specially painted by an artificial colour. Such a method permits localization of heated and cooled tissue parts at the optical topographic map of the investigated area and, thereby, to map the peculiarities of the blood flow at the skin cover.

A functional scheme of a double-channel set-up for the realization of the above method is also known. The set-up includes thermovision system, fulfilled on the basis of a commercial thermovisor, which is connected via interface board with a computer system. The set-up has also an illumination source, an ordinary video camera and a block for combining of thermovisor images with that of video camera at display of a video controller.

This method also has considerable disadvantages. At the prototype, optical mapping is performed with the use of video camera and is assigned to improve the spatial resolution of the investigated region image. Under these conditions, a very useful information is absolutely lost concerning the dynamics of the tissue blood supply processes which is contained at the optical image of the visual and near infrared spectral regions. At the same time, it is known that optical images, recorded at narrow wavelength spectral ranges, brings information on the degree of blood oxygenation, haemoglobin and cytochrome aa3 content, and employment of different wavelengths of visual spectral range gives the possibility of visualization of skin microcirculation at different depths from the surface (for details, see text below). At the prototype, spatial-temporal microcirculation dynamics

is reflected only in the infrared thermo-images dynamics, the depth, the information comes from, being limited by the tissue thickness of not more than 1 mm. Blood flow changes are projected via the temperature conductivity into a very thin, less than 100 um, near surface epidermis layer. The latter itself does not contain blood capillaries, but only radiates infrared radiation in accordance with the thermo-projected temperature distribution. Besides, such visualization method of microcirculation dynamics is inertial one, since the thermo-projection time comes to several seconds.

The main task of this invention is elimination of the disadvantages of the prototype, i.e. increase in the information volume obtained under the visualization of the spatial-temporal microcirculation dynamics at the expense of :

-an increase in the probing depth up to 3-5 mm and more, together with a possibility of estimation of different depth layers contributions;

-separation of partial contributions of haemoglobin various functional forms, as well as of the other intercellular pigments and water located at the intercellular space ;

-achievement of non-inertial visualization;

-determination of some new physiological parameters, characterizing microcirculation state, microcirculation working cross-section, for example, etc.

This task is solved by additional recording of at least one of the parameters, characterizing interconnection between blood content and capillary blood flow within the method of microcirculation functional diagnostics of physiological liquids in skin, including sequence image recording of the investigated region of skin at the own infrared radiation with simultaneous image recording of the same skin region at scattered light of visual and near infrared wavelength range under conditions of external illumination and with a subsequent superposition of the images obtained; with this purpose at each point of the investigated skin region the relation between temporal changes of the image brightness in scattered light at least at one of the spectral ranges of 0.3 to 2.0 um wavelengths, and changes in brightness of the own infrared radiation is determined and this parameter is represented in the form of spatial-temporal distribution within the boundaries of the investigated region image contour.

At the aforementioned spatial-temporal distributions spatial ranges are revealed, which differ from each other by at least one parameter, characterizing their temporal changes, and a set of such ranges with a similar type of the temporal dynamics of the recorded parameter is represented in the form of a functional map of living organism physiological processes.

An external illumination is performed using a light beam, the distance between the illumination input point and the detection point being periodically changed, recording of image brightness distribution is performed under these conditions synchronously with the frequency of the distance changes.

The invention task is achieved also by inclusion into the apparatus for realization of the suggested method, which consists of an illumination source and transformers of optical and infrared radiation to a video signal, supplied with an optical system and a control block, connected via an interface board with a computer, of an additional selective divisor of the light beam, a block of illumination control and an input-out controller, both transformers having the same optical system, which includes successively placed an input zoom, transparent for optical and infrared radiation, a scanning block and a selective light beam divisor, forming optical and infrared channels; the transformers are placed at the corresponding channels and connected with the interface board via video signals molders, their controlling inputs being connected with the control block of the scanning system, and the block of the illumination control via the input- output controller to the computer.

A block of an analogy dividing could be included into the apparatus, the inputs being connected with outputs of transformers of optical and infrared images to video signals, and the output - to input of video signal former; discrete photodetectors connected with video signal molders could be used, as the transformers of optical and infrared images to video signal, and discrete photodetectors could be united into arrays.

A modulator of illumination frequency and synchronous detectors one for each photodetector could be additionally included into the apparatus, the modulator output is connected in this case with input of illuminator control block and inputs of the synchronous detectors are connected with outputs of discrete photodetectors, while the corresponding outputs - to inputs of the video pulses molders, output of the modulator synchronizing being connected with the synchronizing input of the synchronous detector.

A modulator of the detected radiation wavelength can be included into the apparatus optical channel and placed exactly before the photodetector, it is coupled with the modulator control block, input of the latter being connected with the input-output controller, and the synchronizing output - with the referent input of the synchronous detector.

The illumination source and/or photodetector of the optical channel, placed at the optical system plane, can be supplied with a driver to produce periodical changes in the mutual distance the latter is coupled with the driver control block, which synchronizing output is connected with referent input of the synchronous detector.

To the optical apparatus channel, an additional photodetector, logarithm amplifiers and a differential amplifier can be included, the photodetector and the illumination source being placed at image plane of the optical system, the photodetectors of the optical channel being connected via logarithm amplifiers with non-invertible and invertible inputs of the differential amplifier and the output - to the input of the video signal molder.

Optical apparatus channel may be a multichannel spectrometer, formed by multielement polychromators and photodetectors, whose outputs via logarithm amplifiers are connected with non-invertible and invertible inputs of the differential amplifiers, and the illumination is produced with a white light source.

The optical channel can contain also two illumination sources, made in the form of light sources lines, and two multi- element lines of photodetectors, placed at the plane of the optical system images in a parallel way to each other, the photodetectors lines being connected with successively connected differential amplifier and video signals molder of the optical channel via logarithm amplifiers, the outputs of the latter being connected with non-invertible and invertible inputs of the differential amplifier; under these conditions the infrared channel photodetector represents also a multielement line, placed in a parallel way to the lines of the optical channel, and connected with video signal molder of the infrared channel via the multichannel amplifier.

The invention is explained by the drawing, where:

fig.1 is a general block diagram of an apparatus for realization of the above described method;

fig.2 is a variant of performance of the signal treatment scheme;

fig.3 is a recording scheme employing spectral modulation and a synchronous detection;

fig.4 is a recording scheme employing modulation of detected radiation spectrum and a synchronous detection;

fig.5 is a recording scheme with the use of arrays of discrete photodetectors;

fig.6 is a graphic representation of distribution of scattered light intensity over the input point of the illuminating beam ;

fig.7 is a recording scheme with the use of a modulation of the observation point coordinate;

fig.8 is a recording scheme with the use of a differential photodetector;

fig.9 is a recording scheme with the use of polychromator and multielement differential CCD structures;

fig. 10 is a recording scheme with one-dimensional illumination sources and corresponding photodetectors.

DISCLOSURE OF THE INVENTION

As it was already mentioned, simple image superposition, equivalent to the linear combination of IR- and optical images, only in an insignificant degree reflects the real interconnection, existing between the capillary blood content and capillary blood flow, which are responsible for brightness (contrast) of optical and IR-ranges, correspondingly. The dynamics of IR-images is influenced not only by the balance between coming to and going out blood flows (arterial and venous circulation branches) but also by the presence of "stagnant reservoirs", "shunting", "blocking" capillary blood flow areas, which, in their turn, determine the contrast of the optical image. Therefore, mutual connection between IR- and optical images is considerably non-linear, on the one hand, and depends on the functional state of living organism, on the other. Consequently, the revealing of such non-linear, "interference" parameters of mutual connectivity of IR- and optical images gives quite a new information, which could not be obtained both separately from IR- and optical image components and from their simple linear combination. However, the non-linear connection exists not only between IR- and optical images, relating to any same point at any each time moment, but also between different points at each time moment and even between different points at different time moments. Such qualitatively higher correlation level could be revealed both with the help of special equipment and more ingeniously, using special software - factor and cluster analysis [4]. Functional images (maps), thus obtained, with a similar functional behavior bring quite a new information about living organism functioning as one and same system, or about the hierarchy of large interconnected subsystems. They could not be obtained by any other way, but only with the use of a thermovisor, a video camera, the images combination and a computer supplied with a corresponding software.

Fast (less than 1 s) blood vessel reactions on any external influence are revealed first of all at the optical image brightness: under the vessels constriction (dilating) optical image brightness decreases (increases). In addition, the vessels passage capability is also changed, while blood pressure at the main artery is unchanged. As a result, blood flow is correspondingly changed and variations in the dynamics of IR- images brightness appeared with a time delay of several seconds being equal to the above mentioned thermo-projection time. At the presence of some physiological disturbances, a synchronous behavior of IR- and optical images brightness is broken and their ration is not already a

constant value. This permits determining the localization and the character of the vessels pathology.

Another additional example, characterizing the above mentioned interconnection, is time delay (exceeding the above thermo-projection time) between the equivalent parts of the temporal dynamics of IR- and optical images brightness for each point.

If extrema are looked for and followed not in time (for each spatial point), but in space (for each time moment), then spatial- temporal distribution of such extrema describes a third type of parameters characterizing IR- and optical images interconnection.

To separate from artifacts the signals due to blood microcirculation (or any other physiological liquid) at some depth from skin surface, a method of wavelength, λ -modulation can be applied. Such artifacts could be provoked by light reflecting from the surface, by fluctuations of the illuminating beam intensity Io (r,t), by external illumination, by skin pigmentation, by water absorption, by light scattering in epidermis, by a light-shadow distribution, F (r,t) etc. Method of λ- -modulation includes recording of the difference in the intensity distributions for the reflected light dI(r,t) for two different wavelengths. The latter are chosen so that physiological pigments (haemoglobin, for example) have significantly different absorption characteristics and, consequently, different diffusive reflectivity, described by function, f. If these wavelengths are not considerably different, then for the other above described factors, determining image brightness and only slightly depending on the wavelength, λ , their spectral dependency could be neglected. Then

$$I(r,t) = Io(r,t) \times F(r,t) \times f(\lambda, c, r,t)$$

$$dI_{\lambda_1,\lambda_2} = Io \times F \times df$$

(r,t, factors independent of λ ; c, physiological pigment concentration)

and the ratio dI/I = df/f describes only the pigment investigated.

Wide possibilities of the method are realized under recording of the optical images at discrete wavelengths of visual optical range.

It is possible, taking into consideration spectral dependence of the reflective capability (R=I/Io) of biological tissues [5], to separate several spectral intervals where the most considerable changes in the absorption coefficient, coefficient of back scattering and reflective capability take place. At the spectral range under consideration, the reflective capability is determined only to a small extent by Frenel surface reflection (Rsur =4 - 6%) and the main contribution is made by back scattered radiation (Rback.sc.) from the depth tissue , where the main physiological pigments, haemoglobin, in particular, and water are located. The selection of the signal connected with the tissue blood content is convenient to perform with the help of the aforementioned frequency modulation of the illuminating radiation at spectral ranges of a strong spectral dependence of physiological pigments absorption, of haemoglobin especially, since optical absorption of epidermis is very small and only slightly depends on the radiation wavelength. The modulation of illuminating radiation wavelength results in an amplitude modulation of radiation, reflected from the tissues, containing physiological pigments; the latter radiation is recorded by synchronous detecting at the modulation frequency of illuminating radiation. Under these conditions spectral band of radiation used must be less than frequency (wavelength) interval, over which the modulation is performed.

To perform recording of the total oxygenated and deoxygenated haemoglobin content in tissues of up to 3 mm depth, the radiation frequency (wavelength) is modulated at a spectral range near 0.59 um, the minimal wavelength being chosen at 0.53 um to 0.58 um wavelength interval (the long wavelength haemoglobin absorption band), and the maximal one - from 0.6 um to 0.63 um. To record haemoglobin content at a lesser depth, the modulation is performed near 0.43 um wavelength, the minimal wavelength being chosen at 0.38 um - 0.43 um wavelength interval (Sore band of haemoglobin absorption), and the maximal one - from 0.46 um to 0.50 um.

To record the partial concentration of deoxygenated haemoglobin, the λ - modulation is performed near 0.68 um wavelength, where oxy-haemoglobin absorption is minimal (frequency derivative is equal to zero). The modulation interval is from 0.63 um to 0.72 um.

Oxy-haemoglobin absorption is a dominant one at 1.03 um - 1.1 um wavelength interval. As a referent interval for a choice of minimal wavelength, 0.8 - 0.9 um interval is used since here the absorption is minimal and does not depend on oxygenation degree of haemoglobin, while the reflective capability is maximal.

To record water concentration at near surface tissues (under the conditions of uniform illumination up to 3 mm depth) the wavelength near 1.15 um at the interval of 1.1 to 1.2 um is modulated.

Water content at still lesser depth (at a horny epidermis layer) could be estimated via absorption at spectral window of 1.6 - 1.8 um, under these conditions, as a referent wavelength, 1.4 um and 1.9 - 2.0 um wavelengths are used, where the reflective capability is minimal and is determined practically by Frenel,s surface reflectivity.

Of a special interest, is the possibility of hematocrit estimation as a ratio of haemoglobin and water concentrations at near surface tissues, by means of a comparison of the results of haemoglobin concentration measurements at the spectral range of 0.53-0.63 um and those for water at 1.1 - 1.2 um wavelength range. At these wavelength ranges the reflected radiation is formed by back scattering in tissues of practically the same thickness (the geometry of diffusive scattering for these interval is similar). Analogous possibility of hematocrit estimation appeared when the results of haemoglobin concentration measurements at 0.38 - 0.50 un wavelength interval are compared with those for water at 1.3- 1.4 um wavelengths.

It is possible, instead of modulation of illuminating radiation wavelength , λ, to employ illumination with spectral band wider than the modulation intervals, and to modulate the receiving spectral band of the photodetectors with a subsequent synchronous detecting of appearing amplitude modulated signal.
As for the technical result achieved, such a mode is completely equivalent, to that involving the λ - modulation.

BEST MODE OF THE INVENTION REALIZATION

The method can be realized with the help of an apparatus shown in a schematic form in fig. 1.

Surface 1 of a subject is illuminated with the help of illuminator 2, managed by the illuminator control block 3, permitting regulation of the illumination brightness and spectral composition. Radiation, scattered by the subject surface, as well as the subject own IR-radiation are recorded by detecting device 4. This device includes an input optical scanning system, consisting of input zoom 5, scanning block 6, selective divisor 7 of the illumination beam. Radiation of IR-channel is recorded by photodetector 8, and that of the optical channel - by photodetector 9. Elements 5 and 6 are capable to transmit radiation of both the wavelengths ranges. Selective divisor 7 transmits IR-radiation and reflects the optical one.

Electric signals from photodetectors 8 and 9 outputs are received by corresponding amplifiers 10 and 11 and then by corresponding video signals molders 12 and 13. Synchronizing pulses are brought to the video signals molders from output of control block 14 of the scanning system. Block 14 performs controlling of scanning block 6 function and forming of the frame and row synchronizing pulses.

Video signals of the two channels, formed at blocks 12 and 13, are received via interface board by computer 19, performing the subsequent data treatment. With the help of the same computer, the management by the illumination control block 3 is performed through input-output controller 17.

The method is performed as follows. To record the parameters, characterizing interconnection between blood content and blood flow, a subject is illuminated by radiation of the source 2, the radiation wavelength being at one of the aforementioned intervals in the range 0.3 - 2.0 um. Radiation, reflected by the subject surface 1, i.e.by skin, together with own IR-radiation is received via input zoom 5 by scanning block 6 and is divided by selective divisor 7 into two flows. One flow (infrared) is registered by photodetector 8 and the other (optical) is recorded by photo- detector 9. Photodetectors 8 and 9 are placed so that they could record radiation originating from the same point of the subject. Scanning block 6 provides a subsequent examination of all surface 1 points, being at the detector 4 range of vision. The sequence of electrical signals from amplifiers 10 and 11

is divided into rows and frames with the help of synchronizing pulses, coming from the control block of the scanning system. In such a way, video signals of IR- and optical wavelength images are formed at blocks 12 and 13. The latter signals are received by interface board 15, transforming them into digital form and performing the functions of input, output and image accumulation. The final image treatment, i.e. functional maps construction, is performed at computer 16.

In fig. 2 a variant of a scheme of the signal treatment is presented. The peculiarity of this scheme is the use of analogy divisor 18. It is placed between the outputs of amplifiers 10 and 11 and input of video signal molder 12. Divisor 18 is destined for calculation of the amplitude ration of IR- and optical signals. In such a case, an image is formed at the computer display describing temporal changes of infrared radiation intensity as compared with those of the optical one for each surface point.

Fig 3 shows a scheme of image recording with illuminating radiation modulation and a synchronous detection. To perform this mode, illuminator 2, managed by control block 3, radiates light of λ_1 and λ_2 wavelengths alternatively with the frequency of over- switching, fm (the concrete values of λ_1 and λ_2 are set up on the basis of the spectral ranges necessary to provide a definite probing depth). The modulation frequency must be much larger than the reversed scan time of a single image element. For example, under image discretization 128 x 128 elements and frame frequency of 50 Hz, one image element is taken for a time interval equal to 1/(128 x 128 x 50) = 1.2 us, it means that fm should be Larger than 3 - 5 MHz.

Between output of amplifier 10 of the optical channel and input of the corresponding video signal molder 12, synchronous detector 19 is included. Referent signal, synchronous with the frequency of fm, is formed in modulator 20, connected with input of control block 3, it is received by referent output of synchronous detector 19. The latter separates signals of frequency fm with amplitude being proportional to the wavelength derivative of the light reflectivity coefficient. When the necessary spectral interval is chosen, this signal brings information on the dynamics of the corresponding blood component (oxy-, deoxy-haemoglobins, cytochrome aa3 and water) concentration changes.

Fig.4 presents a recording scheme employing spectral modulation of the recorded illumination and a synchronous detecting, as in the case of a wide band illumination. To perform such a regime, before input of the optical channel photodetector 9, modulator 21 of recording wavelength, connected with block 22 of the modulator control, is placed. Synchronous detector 19 is included between amplifier 10 output and input of the corresponding video signal molder 12, to the referent input of detector 19 signal from modulator control block 22 is coming. This scheme functions similarly to that shown in fig.3.

In fig. 5 a recording scheme employing arrays of discrete photodetectors is shown. Such a scheme gives the possibility to simplify scanning block construction, moving the beam over a single coordinate for the case when arrays of the photo- detector elements are one-dimensional. In the case when a two-dimensional arrays are used, the scanning block could be excluded at all, or a mechanic scanning with much lower rates may be applied. Photodetector 8 of the thermal channel is an array of discrete photodetector elements 23, and photodetector 9 of the optical channel is also an array of the elements 24. Outputs of elements 23 are connected with the corresponding inputs of the multichannel amplifier 25, each of the channels serving as an amplifier 11. Outputs of multichannel amplifier 25 are connected with inputs of video signal molder 13 of IR-channel.

Outputs of elements 24 are connected to inputs of multichannel amplifier 26, each of the channels being amplifier 10. Outputs of amplifier 10 are connected with inputs of multichannel synchronous detector 27, consisting of elements 19. The referent signal for each of the detectors 19 is formed at block 22. Outputs of elements 19 are connected with inputs of video signal molder 12 of the optical channel.

All the subsequent realizations of the method are based on a strong dependence of the scattered radiation intensity on the distance between the input point of the illuminating beam and the point of the scattered light output (the observation point), for this purpose, the illuminator, contrary to the variants with a uniform illumination shown in fig. 1-3, forms light beams of different intensity. In fig. 6 a diagram of the intensity distribution I(r) is shown: an input point of the illuminating beam is marked by 28 and the observation point by 29. By choosing the observation point, shifted

relative the illumination point by several photon transport lengths at the tissue investigated (more than 5 mm), and by periodically changing the distance between these points, it is possible to receive signal at the modulation frequency, depending only on the state of the depth blood containing skin layers and not depending on parasite effects (for the case under the consideration) of scattering and absorbency at the horny epidermis layer at the point of the illuminating beam input. It is possible to perform the variation of the distance between points 28 and 29 by two means: by shifting the illuminating beam input while the observation point is fixed or vice versa. Under these conditions the observation point of IR-channel should be located between the input and the observation points. The case of changing of the observation point is shown in fig. 7. Moving of the observation point from one outermost position 29 to the other 30 is performed by moving the photodetector at the image plane to the corresponding direction by the corresponding distance. Such moving could be performed with driver 31 of pull-push movement, connected with block 32 of the driver control. A similar driver 33 may be connected also with illuminator 2, in the latter case driver 31 should be switched off. Illuminator 2 and photodetector 9 of the optical channel are located at the image plane.

Observation point 29 must be shifted relative to point 28 (fig. 7) in such a way that the point of the scattered light receiving is located at the exponential part of I(r) function (position 34 of fig. 6). Function I(r) may be expressed in an analytic form as follows:

$$I(r) = I_0 f(r, \varkappa) \exp[-\varkappa (r - r_0)]; \quad \varkappa = \sqrt{3 \sigma_p \sigma_n N^2}$$

σ_p, σ_n – absorption and scattering effective cross-sections of erithrocytes;

N – erithrocytes concentration;

$f(r, \varkappa)$ – a function, slightly dependent on the beam coordinate;

r_0 – coordinate of the beam input.

Then $\ln I(r) = \ln I_0 + \ln f(r, \varkappa) - \varkappa (r - r_0)$.

When the coordinate of the observation point is shifted by Δr, then the corresponding change in $\Delta \ln I(r)$ is as follows:

$$\Delta \ln I(r) = \frac{\Delta I(r)}{I(r)} \approx - \varkappa \cdot \Delta r$$

Consequently, measurement of $\Delta \ell n I(r)$ via the mode of coordinate r modulation gives the possibility to calculate parameter $\mathcal{L}$, as well as connected with this parameter erithrocytes concentration. This means that the logarithm derivative of the reflected signal permits determining parameter $\mathcal{L}$, and thereby, the state of microcirculation of physiological liquids at the investigated layer.

For a technical realization of the logarithm derivation, the signal at the frequency of the modulation comes to logarithm amplifier 35, connected with synchronous detector 19 and then, as in previous variants shown in fig. 3 - 5 , to video signal molder 12. In this case the referent signal for detector 19 is produced by the driver control block 32.

In fig. 8 a variant of the apparatus is shown where the logarithm derivation is performed by a differential photo- detector. The latter contains two one-element photodetectors 9 fixed at holder 36 together with illuminator 2, both are placed at the optical system image plane. The distances between the photodetectors are chosen so that the observation points 29, 30 are separated by distance Δr. Photodetector 9 outputs are connected with logarithm amplifiers 35 and 37 inputs. Outputs of the latter amplifiers are connected with invertible and non- invertible inputs of differential amplifier 38, output of the latter being coupled with video signal molder 12.

Thus, the measurements employing differential photodetector give information about parameter $\mathcal{L}$. In this case, unlike that shown in fig. 7, the use of λ -modulation is more convenient and straightforward. Under these conditions the detection is performed at the frequency of λ -modulation, unlike the previous case , where it is carried out at the beam spatial modulation frequency. When a scheme shown in fig.7 is employed, combination of the two modulation modes is possible only if the frequencies of the modulation are sufficiently different and a double synchronous detection is carried out.

Fig. 9 shows a recording scheme including polychromator and differential multielement photodetectors on the basis of CCD structures. Such a scheme makes it possible to obtain temporal behavior of the reflected light not only at some fixed wavelength, but also in a wide

spectral range. As a result, separation and identification of contributions to the total signal from different components of physiological liquids could be brought about, the distribution of some solute medicinal components, for example. A wide spectral range of the illuminating radiation is secured by illuminator 2, consisting of white light source 39 and lens 40. The latter focuses light of the illuminator into input hole 41, made at plate 42, which is located at the plane of the detector image. Image of this input hole at surface 1 of the subject investigated is the illuminating beam input point 28.

Output holes 43 and 44 correspond to observation points 29 and 30, via these holes the light beams come to polychromator 45. After coming through polychromator 45, the white light is decomposed on the spectral components spreading at different directions. Each of such components is recorded by separate element 46 of multielement photodetectors 47 and 48. Each of photodetectors 47 and 48 is connected with logarithm amplifiers 35 and 37 inputs, the outputs of the latter being connected with inputs of differential amplifier 38. Further, as in previous variants, signal is received by video signal molder 12 input and so on.

Fig. 10 shows a variant of the apparatus employing one- dimensional illumination sources and detectors. Such a device makes it possible to avoid the necessity of row scanning and to use only the frame one, since at each time moment recording of two lines of television scan - the main and differential (shifted at the objective plane relative to the main) ones is performed. This technical way gives the possibility to reduce time of frame recording and, thereby, provides the conditions for recording of fast processes, improves the signal/noise ratio, while one frame recording time remains the same. In addition, avoiding of row scan results in a considerable simplifying of scanning and synchronizing optico-mechanical systems construction.

In such construction, lines 49 and 50 of illuminators, radiating at wavelengths λ_1 and λ_2, correspondingly, as well as lines 47 and 48 of the photodetectors are fixed at holder 36, located at the optical system images plane, the distance between lines 49 and 50, 50 and 47, 47 and 48 are chosen so that shifts at the plane of the subject between images 51 and 52 of the illuminator lines 49 and 50, as well as between observation lines 53 and 54 satisfies to the following relations: $\Delta_{51-52} \ll \varkappa^{-1}$; $\Delta_{52-53} \sim \varkappa^{-1}$; $\Delta_{53-54} \sim (0.2 - 0.5)\,\varkappa^{-1}$.

Each of detectors 47 and 48 is connected with logarithm amplifiers 35 and 37 inputs, while output of the latter - to inputs of differential amplifier 38. Then signal, as in previous variants, comes to input of video signal molder 12. The lines 49 and 50 are connected with the illuminator control block 3. In such a mode, IR-detector 8 should also be a one - dimensional multielement line, consisting of discrete elements 55, capable of recording the whole frame line at each time moment. A device of the signal processing from such a multielement detector is similar to that shown in fig. 5.

At the display of video control device an image of the investigated subject surface is reproduced in a monochrome, for example, white-black colour. At its background, the regions with a similar character of dynamic microcirculation behavior of physiological liquids in skin are marked out with the help of pseudo-colours. The distribution of the colour brightness reflects the distribution of the corresponding pigment concentration at the near surface skin layer.

Elements of the optical channel must secure the possibility of working in a wide wavelength range, they could be prepared, in particular, from quartz, sapphire, i.e. materials transparent enough both for visual and IR-wavelength ranges. As a selective divisor, a germanium or silicon plates could be used. A dichroic mirror could also be used as such a divisor. The scanning scheme could be made according traditional mirror scheme, widely used in construction of thermovisor devices [6].

As an interface board, it is possible to use known video microprocessors for computers, performing images input and visualization [7], that of DT 2803-60 of DATA TRANSLATION, in particular.

Block 3 of the illuminator control sets up following the computer system command the necessary intensity level and the spectral composition of illumination, either for one common source of optical radiation or for each of several separate sources, and with the help of input-output controller performs switching on one or another source or of the sources groups. The constructive principle of such a system is known in technology, and is used, for example, in scene illumination shows, so it is not considered in this invention.

As a driver of push-pull illuminator and/or photo-detectors moving, a linear piezo-electric engine may be used securing practically non-inertial work at a wide shifting range [8].

As an illumination source, incandescence lamps may be applied, as well as light diodes and other sources of visual and IR-radiation.

THE INVENTION FORMULATION

1. A method of investigation of functional dynamics of physiological liquids in skin, confining in image sequences recording of a skin area in its own infrared radiation with a simultaneous image recording of the same skin area in the scattered light of visual or infrared wavelength range under the conditions of external illumination with a subsequent superposition of images thus obtained, d i s t i n g u i s h i n g by an additional recording of at least one of the parameters characterizing interconnection between blood content and capillary blood flow; for this purpose, at each point of the skin area investigated the ratio between temporal changes in the image brightness at scattered light at least at one of the spectral intervals from the wavelength range of 0.3 - 2.0 um, and changes in brightness of its own infrared radiation, is measured; the latter parameter is represented in the form of its spatial- temporal distribution in the framework of the investigated skin area image contour.

2.A method as described in claim 1, d i s t i n g u i s h i n g by revealing at the aforementioned spatial-temporal distributions of the spatial regions differing one from another by at least one parameter, characterizing their temporal changes and by a representation of a set of such regions with a similar type of temporal dynamics of the recorded parameter in the form of a functional map of physiological processes of living organism investigated.

3. A method as is described in claims 1,2, d i s t i n g u i s h i n g by employment, as an external illumination, of a light beam, the distance between the point of its input and the detection point being periodically changed and image brightness distribution recording being performed synchronously with the frequency of the distance changes.

4. An apparatus for realization of the method as described in claims 1 - 3, including transformers of optical and infrared images into a video signal, supplied with an input optical system, having a control block, and connected via an interface board with a computer, and an illuminator, d i s t i n g u i s h i n g by an additional inclusion into the apparatus of a selective light beam divisor, an illuminator control block and an input-output controller, both transformers having the

same optical system, including successively placed an input zoom, transparent for optical and infrared radiation, a scanning block and a selective light beam divisor, forming optical and infrared channels; the transformers are placed at the corresponding channels and connected with the interface board via video signals molders, control inputs of the latter are connected with the control block of an electronic scanning system and the illuminator control block is connected via the input-output controller to the computer.

5. An apparatus for realization of the method as described in claim 4, d i s t i n g u i n g by inclusion into the apparatus of an analogy dividing block, its inputs being connected with outputs of the transformers of the optical and infrared images to video signals, and the outputs - to the input of the video signal molder.

6. An apparatus for realization of the method as described in claims 4 - 5, d i s t i n g u i s h i n g by use, as transformers of optical and infrared images into the video signals, of discrete photodetectors, connected via amplifiers with video signals molders.

7. An apparatus for realization of the method as described in claims 4 - 6, d i s t i n g i s h i n g by incorporation of discrete photodetectors into the photodetector arrays.

8. An apparatus for realization of the method as described in claims 4 - 7, d i s t i n g u i s h i n g by additional inclusion into the apparatus of a modulator of illuminating radiation frequency and synchronous detectors one for each discrete photodetector, the modulator output being connected with the output of the illuminator control block, synchronous detectors inputs being connected with the discrete photodetectors outputs, while the outputs - with the video signal molders inputs and the synchronization output of the modulator being connected with the synchronization input of the synchronous detector.

9. An apparatus for realization of the method as described in claims 4 - 7, d i s t i n g u i s h i n g by inclusion into the optical channel of a modulator of the recording radiation wavelength, placed just before the photodetector and connected with the modulator control block, the input of the latter is connected with the input-output controller and the synchronization

output - with the referent input of the synchronous detector.

10. An apparatus for realization of the method as described in claims 4 - 9, d i s t i n g u i s h i n g by employment of a driver to produce periodical changes in the distance between the illuminator and/or the photodetector of the optical channel, both are placed at the plane of the optical system images; the driver is connected with a control driver block, the synchronization output of the latter being connected with the referent input of the synchronous detector.

11. An apparatus for realization of the method as described in claims 4 - 10 d i s t i n g u i s h i n g by inclusion into the optical channel of an additional photodetector, logarithm amplifiers and differential amplifier, the photodetector and the illuminator being placed at the plane of the optical system image, the photodetectors of the optical channel being connected via logarithm amplifiers with invertible and non-invertible inputs of the differential amplifier and the output of the latter being connected with input of the video signal molder.

12. An apparatus for realization of the method as described in claims 4 - 10 d i s t i n g u i s h i n g by realization of the optical channel by means of a multichannel spectrometer, formed by polychromator and multielement photodetectors on the basis of CCD structures, the spectrometer outputs being connected via logarithm amplifiers with non-invertible and invertible inputs of differential amplifiers and the illuminator being supplied with a source of white light.

13. An apparatus for realization of the method as described in claims 4 - 10 d i s t i n g u i s h i n g by the presence at the optical channel of two illuminators, made up a slight sources lines, and two multielement photodetector lines, placed at the plane of the optical system images in a parallel way to each other, the photodetector lines being connected with successively connected differential amplifier and video signals molder of the optical channel via logarithm amplifiers, the outputs of the latter being connected with non-invertible and invertible differential amplifier inputs, the photodetector of the infrared channel being also made in the form of a multichannel line, placed in a parallel way with the lines of the optical channel and connected via the multichannel amplifier with the

video signal molder of the infrared channel.

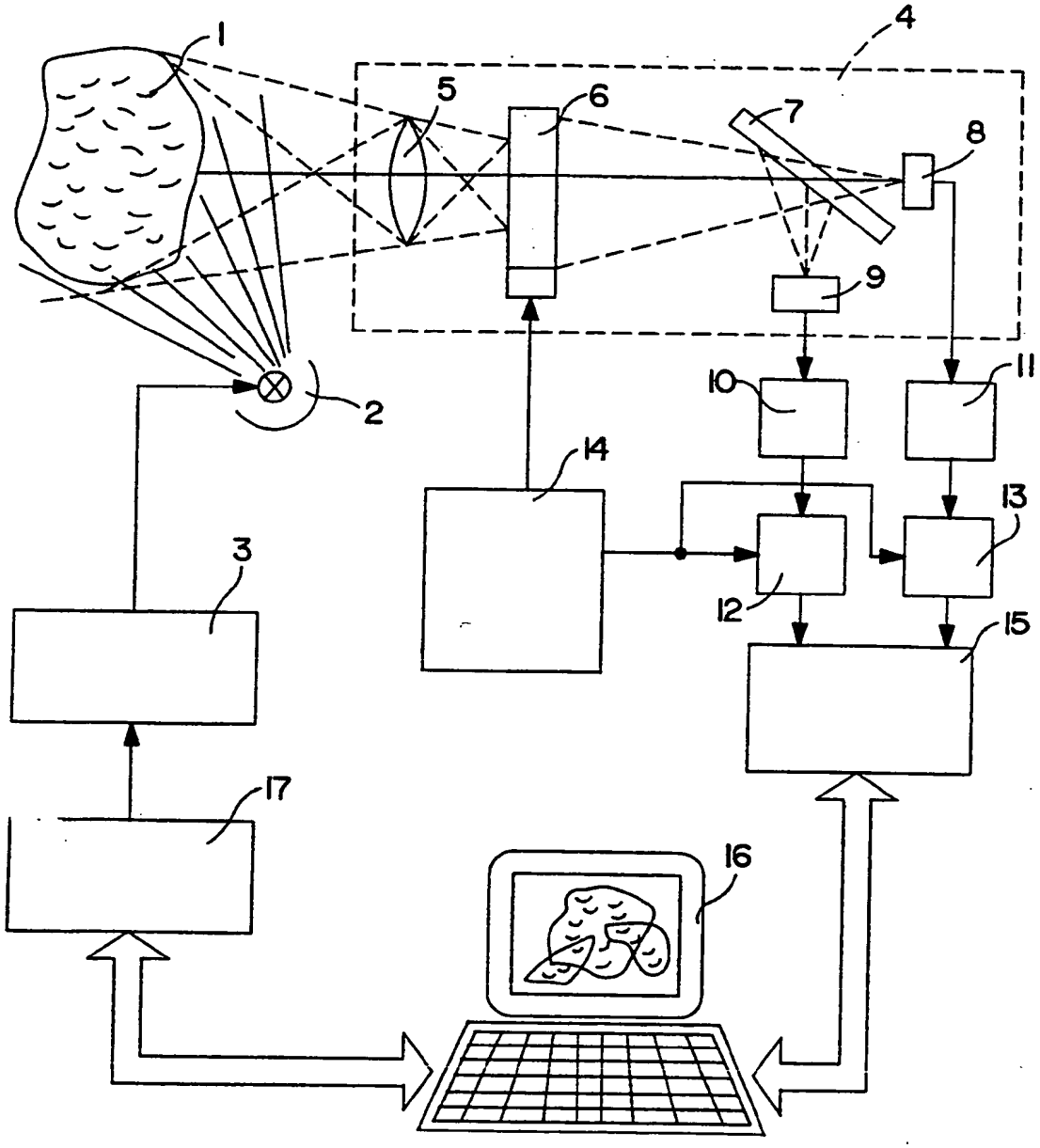


FIG. 1

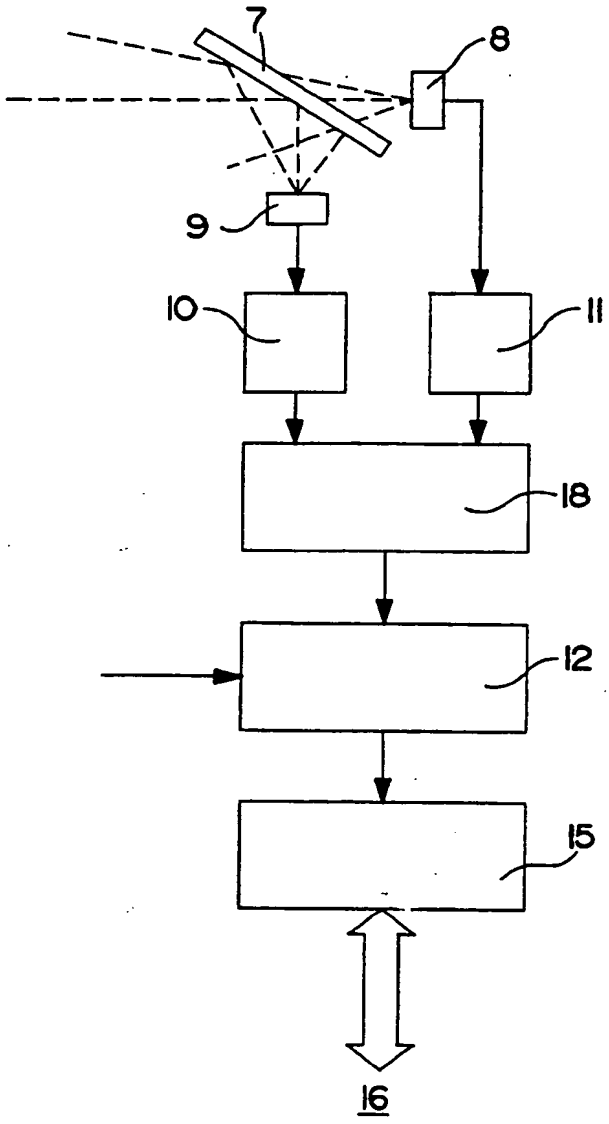


FIG. 2

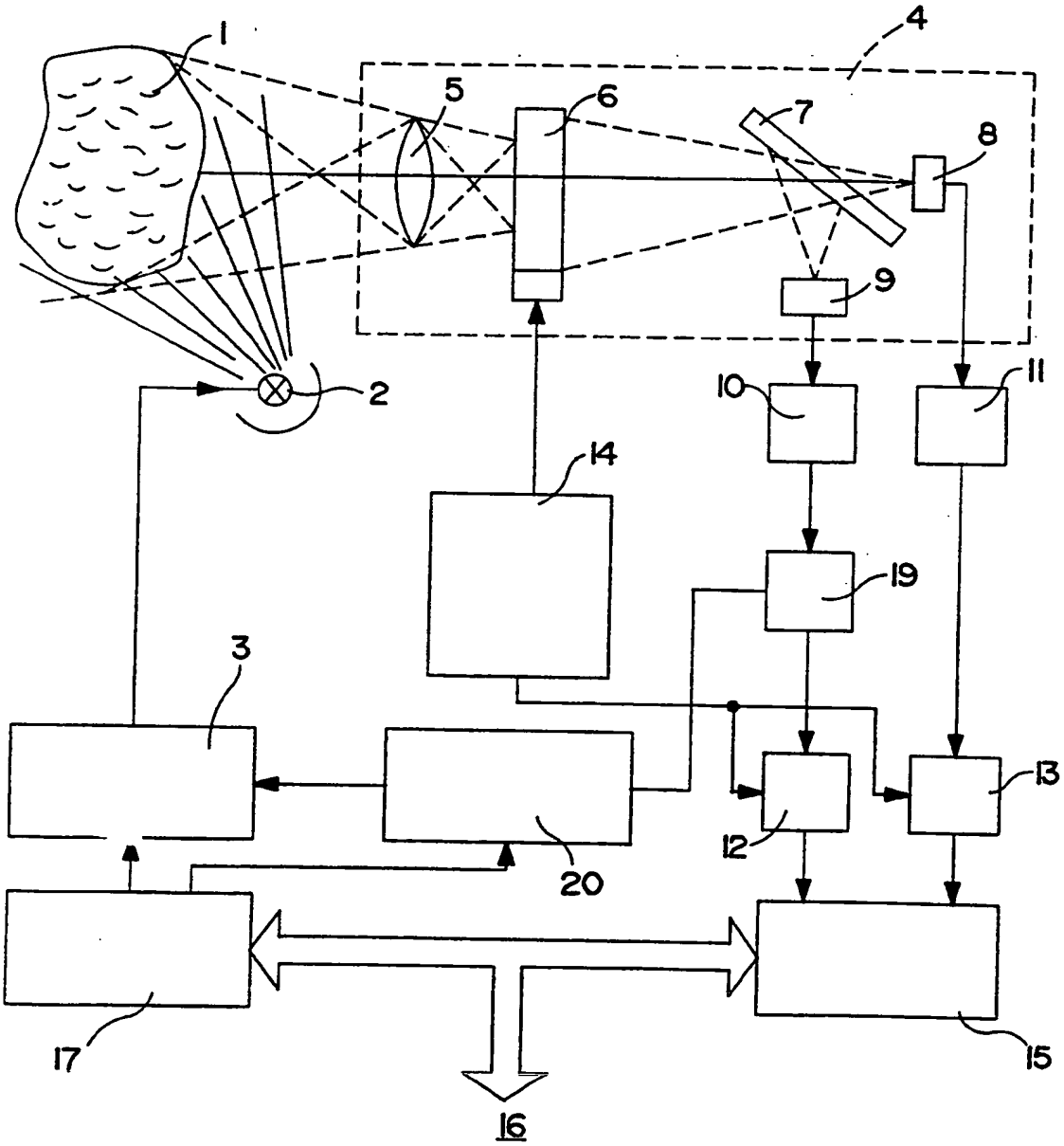


FIG. 3

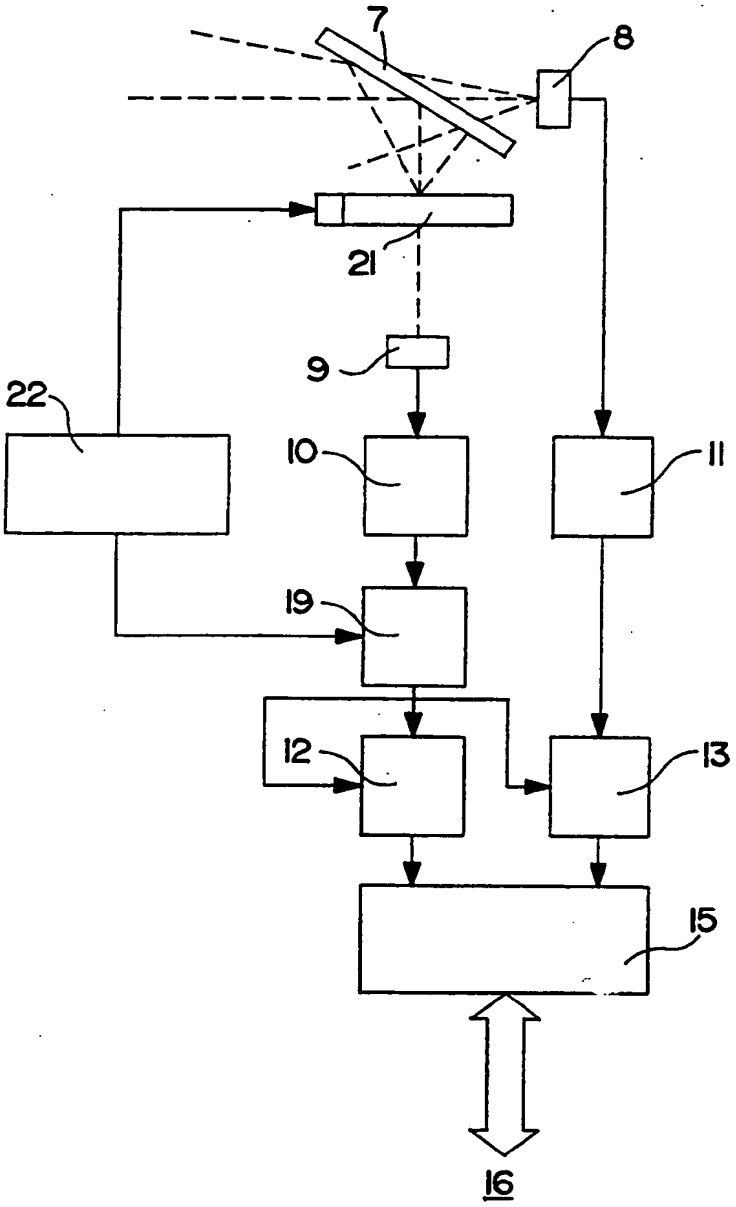


FIG. 4

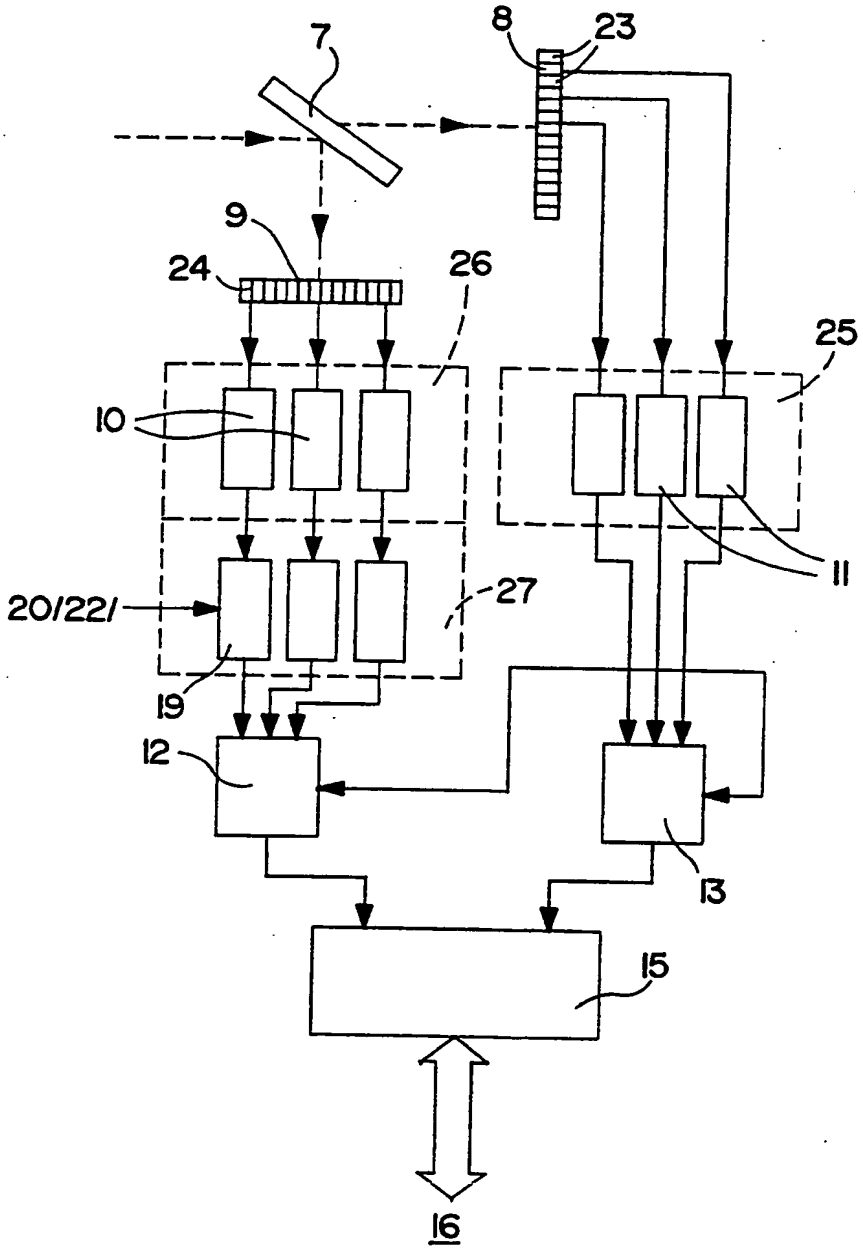


FIG. 5

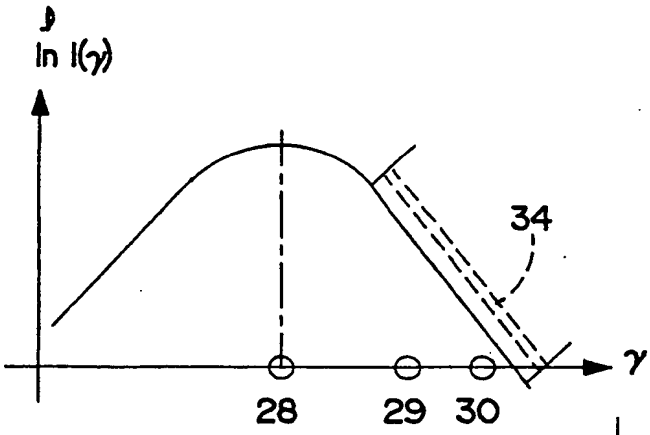


FIG. 6

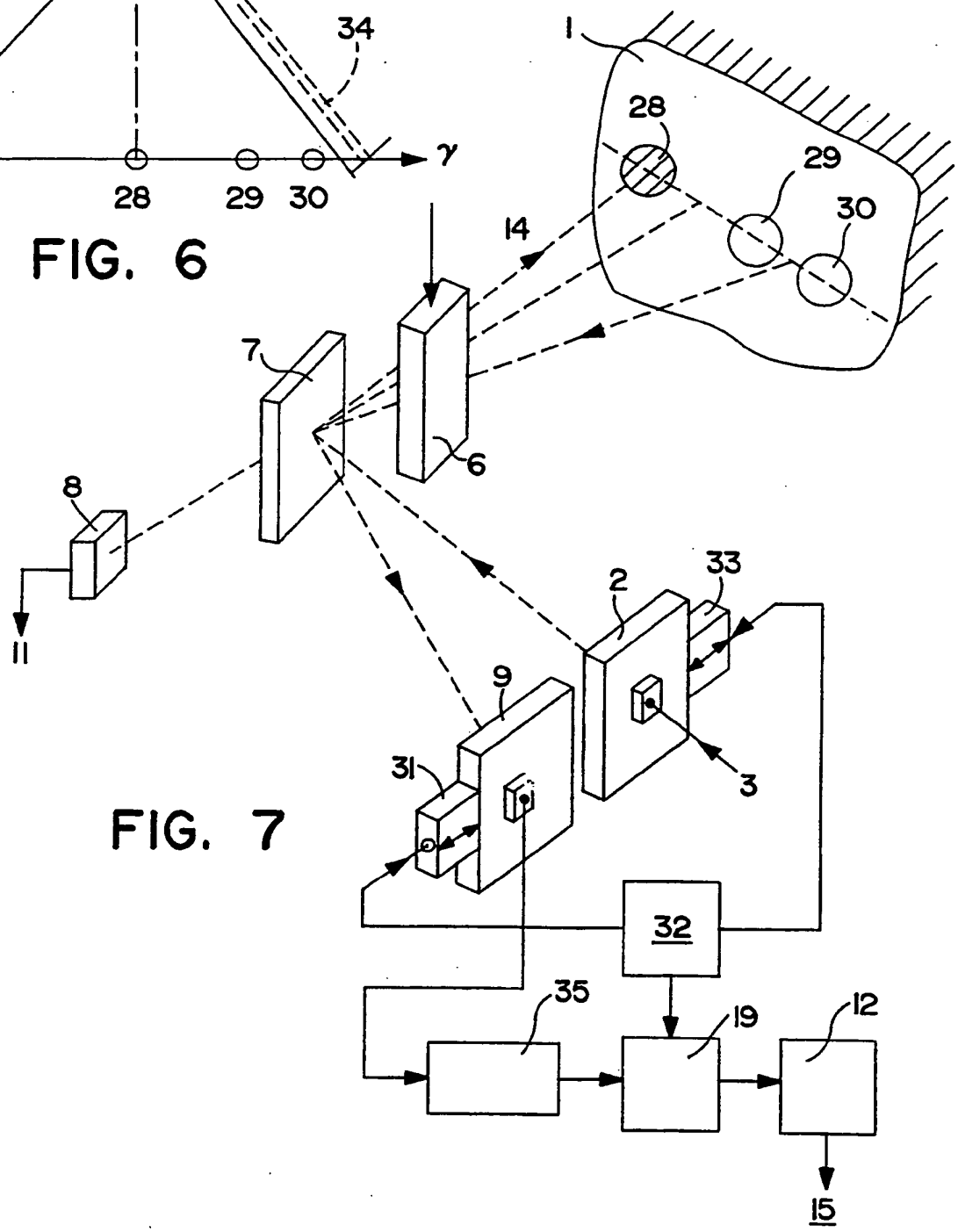
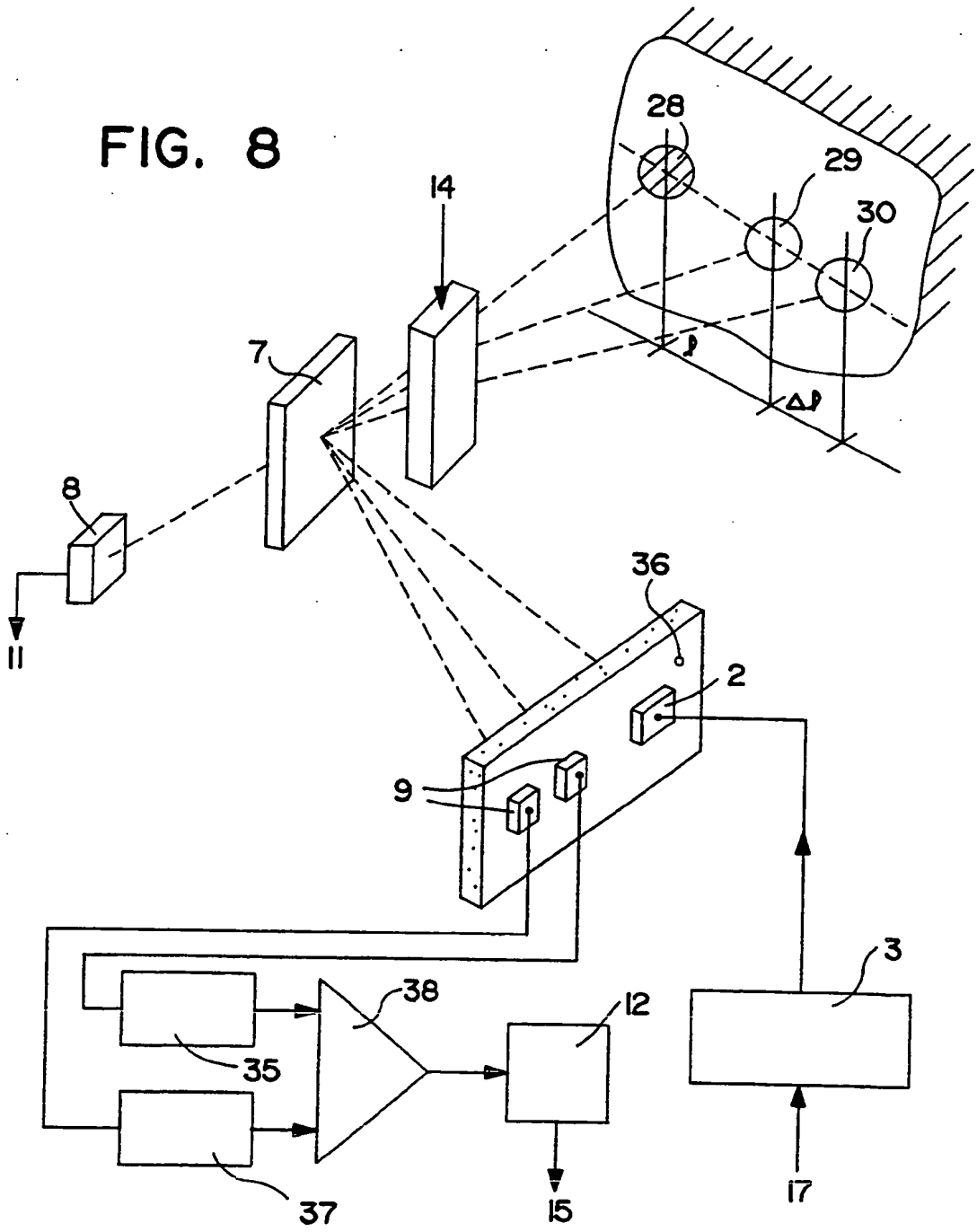


FIG. 7

FIG. 8



SUBSTITUTE SHEET (RULE 26)

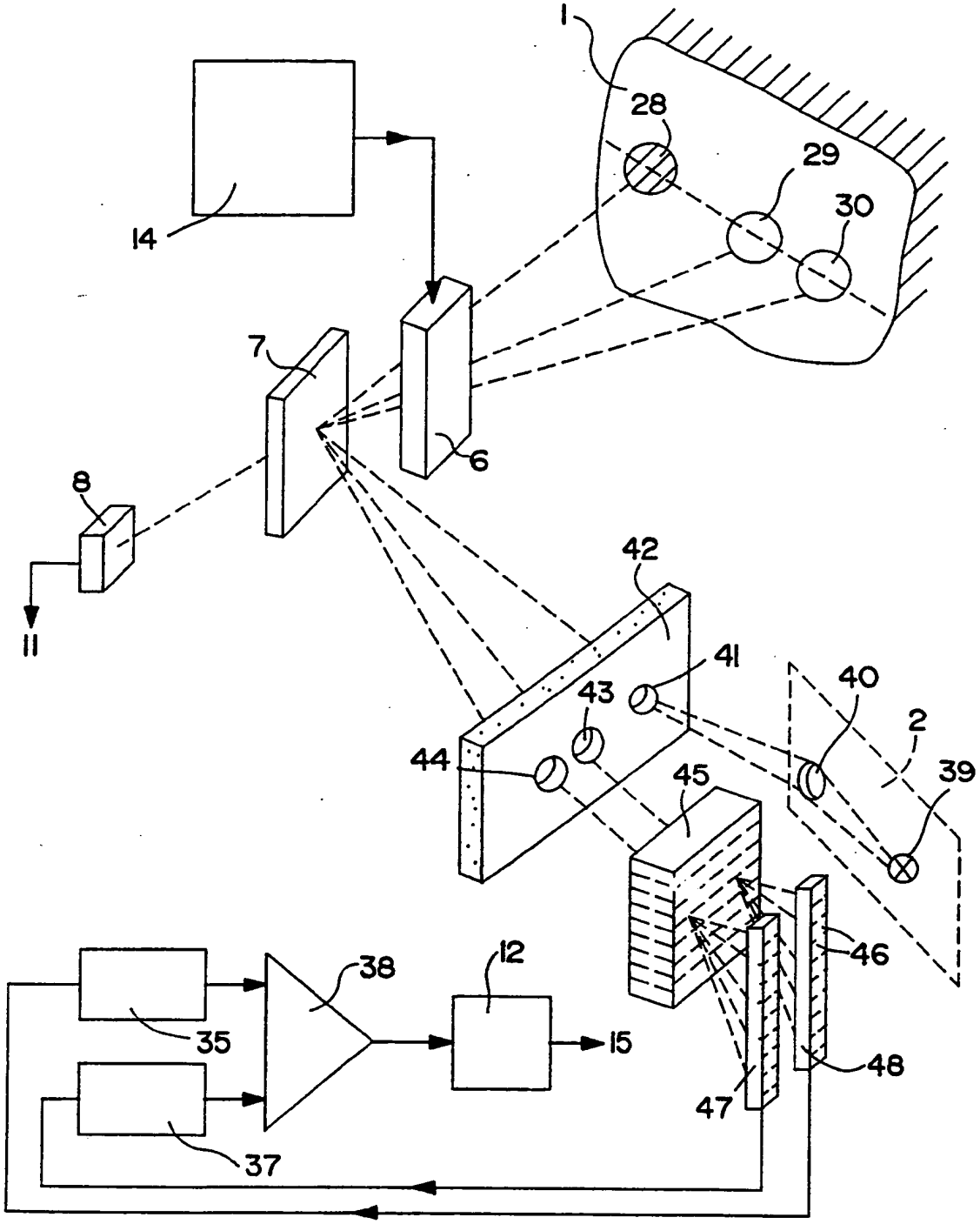


FIG. 9

SUBSTITUTE SHEET (RULE 26)

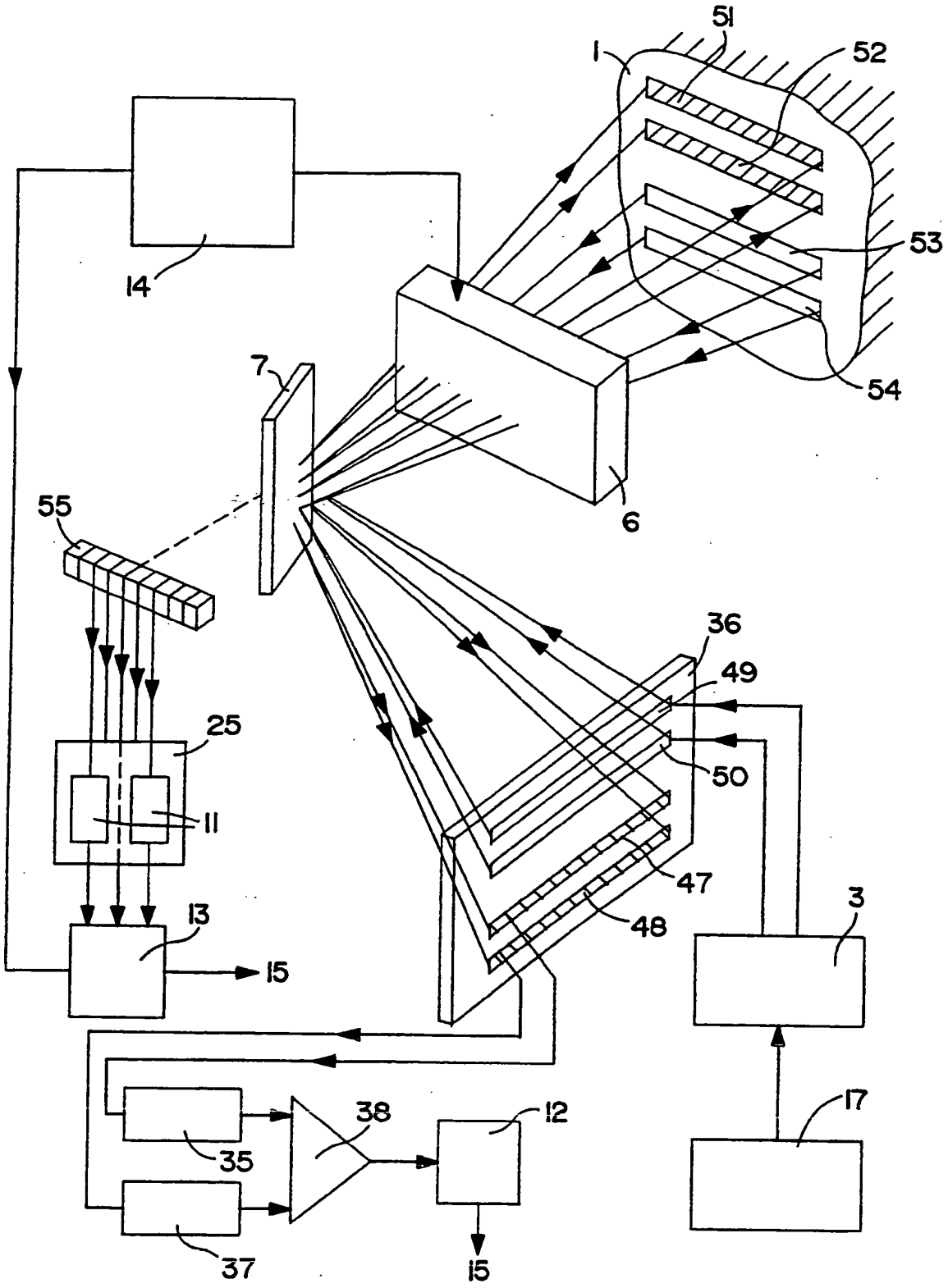


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09480

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61B 5/0295
US CL :128/664, 665

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/632-634,664, 665

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,995,398 (Turnidge) 26 February 1991. See abstract.	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 1994	18 MAR 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer FOR RUTH S. SMITH
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09480

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

It is impossible for the examiner to determine the meaning of claim 2.

3. ☒ Claims Nos.: 3-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.